**Supporting Information**

# Continuous Manufacturing of Cocrystals using Solid State Shear Milling Technology

AUTHOR NAMES

Korde, Sachin[1,2]; Pagire, Sudhir[1,2]; Pan, He[5]; Seaton, Colin[4]; Kelly, Adrian[1,3]; Chen, Yinghong[5]; Wang, Qi[5]; Coates, Phil[3]; Paradkar, Anant[1,2]*

AUTHOR ADDRESS

1. Centre for Pharmaceutical Engineering Science, University of Bradford, Bradford, UK.

2. School of Pharmacy, University of Bradford, Bradford, UK

3. Polymer IRC, Faculty of Engineering and Informatics, University of Bradford, UK

4. School of Chemistry and Biosciences, University of Bradford, Bradford, BD7 1DP.

5. State Key Laboratory of Polymer Materials Engineering, Sichuan University, Chengdu, China

## Table of Content

**SI1 S3M Mill types and details or dimensions**

Table 1: Different S3M mills with different parameters

| S3M type/Parameters | Radius (R) (cm) | Division number (n) | Slot number (m) | Slot top width (δ) | Bevel angle (α) |
|---|---|---|---|---|---|
| S3M 1 | 10 | 8 | 14 | Low | Small |
| S3M 2 | 30 | 8 | 14 | Medium | High |
| S3M 3 | 30 | 8 | 14 | High | Medium |

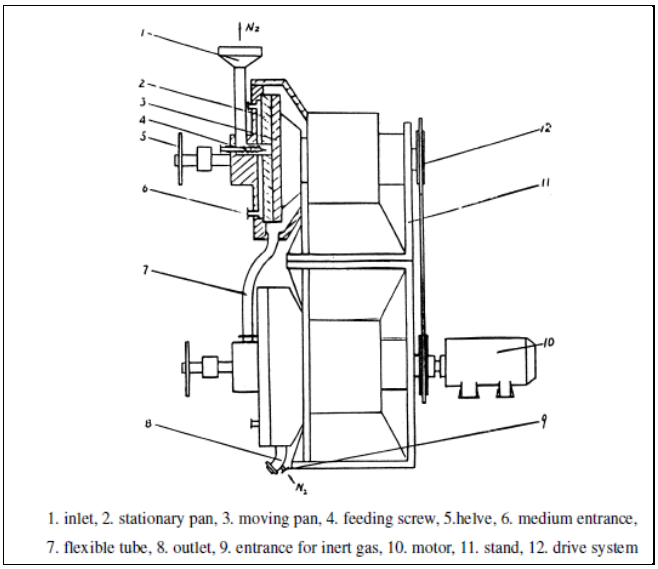


Figure 1: Pan mill equipment design (Xu et al., 1996)

**SI2 DSC findings of CBZ: SAL 1:1 physical mixtures**

Table 2: DSC's of physical mixture of CBZ: SAL 1:1 with various amounts of PEO

| Sr. No. | Polymer and conc. | Eutectic point (°C) | Tg (°C) |
|---|---|---|---|
| 1 | CBZ:SAL 1:1 PM | 139.83, 145.93, | - |
| 2 | CBZ:SAL SOLVENT CC | 159.32 | - |
| 3 | CBZ:SAL 1:1+PEO 5% | 146.04 | 123.79 |
| 4 | CBZ:SAL 1:1+PEO 10% | 146.48 | 120.83 |
| 5 | CBZ:SAL 1:1+PEO 15% | 146.19 | 120.73 |
| 6 | CBZ:SAL 1:1+PEO 25% | 145.79 | 113.29 |

**SI 3 Computational study**

Table 3: Lowest calculated interaction energies between molecular clusters

| System | Calculated Energy (kJ $mol^{-1}$) |
|---|---|
| CBZ-SAL | -354.21 |
| CBZ-PEO | -204.98 |
| SAL-PEO | -222.17 |
| CBZ-SAL-PEO | -547.13 |
| CBZ-2PEO | -515.49 |
| CBZ-SAL-2PEO | -873.37 |

## SI 4 CBZ: SAL 1:1 cocrystal dissolution study and analysis

### 4.1 Dissolution

Drug release for cocrystal batches was studied using USP 2 dissolution test apparatus (Copley Scientific, Type NE4-COP, Serial No. 14355). Samples were analysed using a UPLC analysis method. The dissolution medium volume used during testing was 900 ml at 37°C, deionised water was used as dissolution medium and speed of rotation used was 75. Samples were withdrawn at timely intervals and were subjected to UPLC analysis.

### 4.2 UPLC Analysis

All CBZ: SAL 1:1 cocrystal dissolution studies were analysed by ultra-performance liquid chromatography (UPLC). UPLC gradient method details are as follows,

Column: Waters Acquity column with dimensions of 130Å, 5 um particle size, 4.6 mm internal diameter and 50 mm length

Solvent system: Solvent A: Acetonitrile

Solvent B: deionised water acidified with 0.1% orthophosphoric acid

Injection volume: 50 μL;

Flow rate: 0.6 mL/min.

Wavelengths: CBZ- 285 nm, SAL- 296 nm

Linearity range: 10-100 μg/mL

### 4.3 CBZ UPLC calibration

The UPLC calibration curve for CBZ was linear over concentration range of 10-100 ug/ml. The linearity equation was calculated using calibration curve, slope of the equation was 2146.9, constant 2084.6 and R2 0.9998 (Figure 2). The calibration equation was used to calculate the amount of CBZ released.

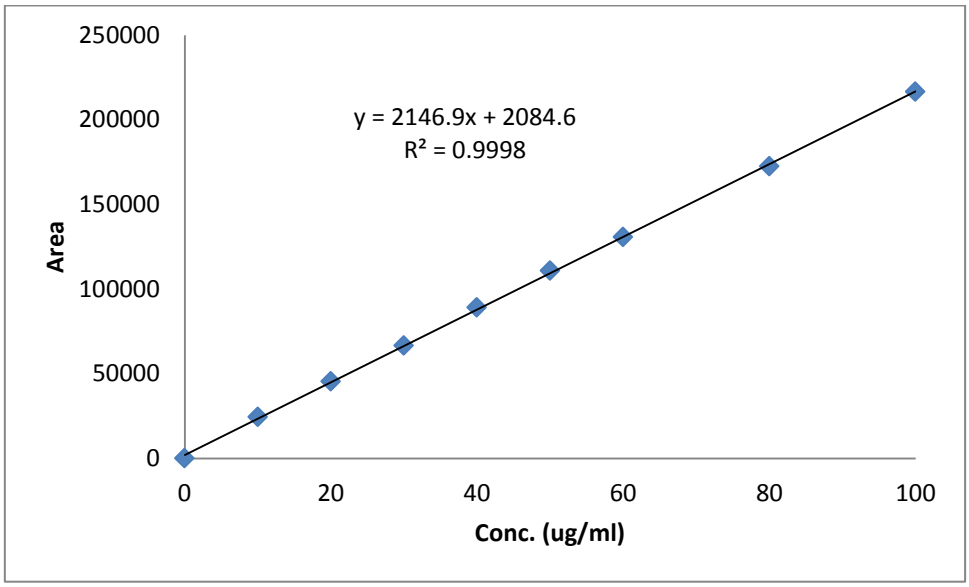


Figure 2. Carbamazepine calibration curve using UPLC at 288nm

CBZ shows a retention time in UPLC of 2.3 mins as shown in Figure 4

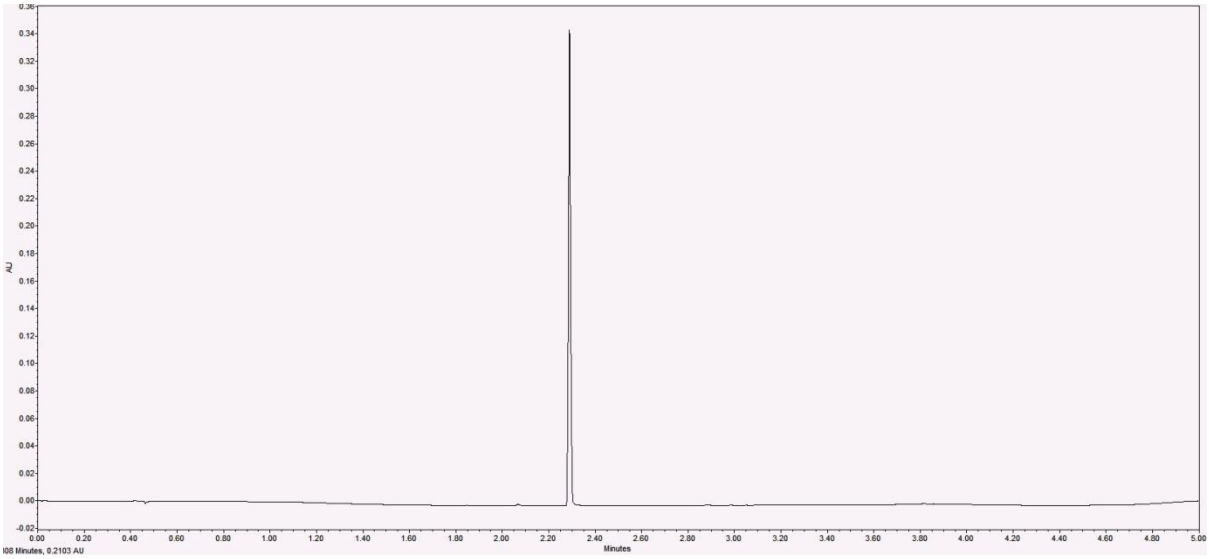

Figure 3. Carbamazepine chromatogram from UPLC analysis

The UPLC calibration curve for SAL was linear over concentration range of 10-100 ug/ml. The linearity equation was calculated using calibration curve, slope of the equation was 998.04, constant -1263.6 and $R^2$ 0.9968 (Figure 4). SAL shows retention time in UPLC at 1.8 min (Figure 5).

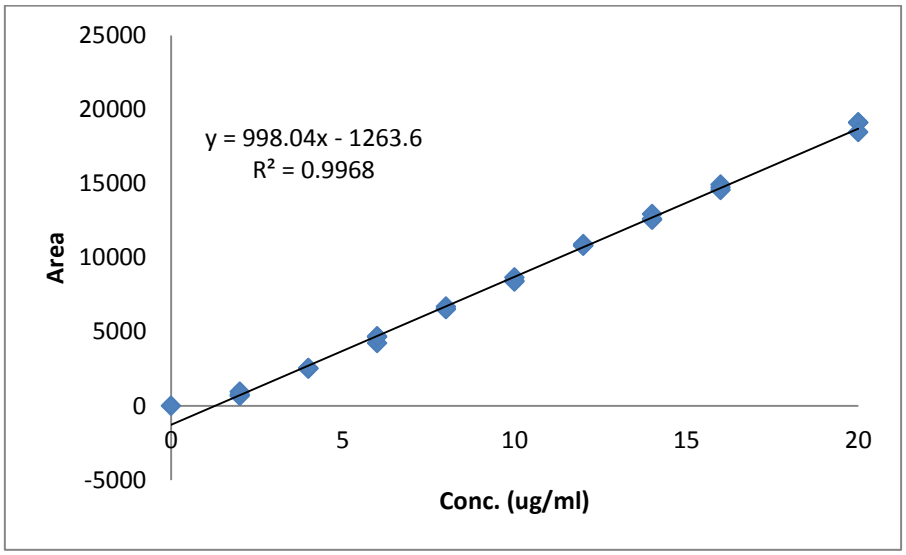


Figure 4 Salicylic acid calibration curve using UPLC at 296nm

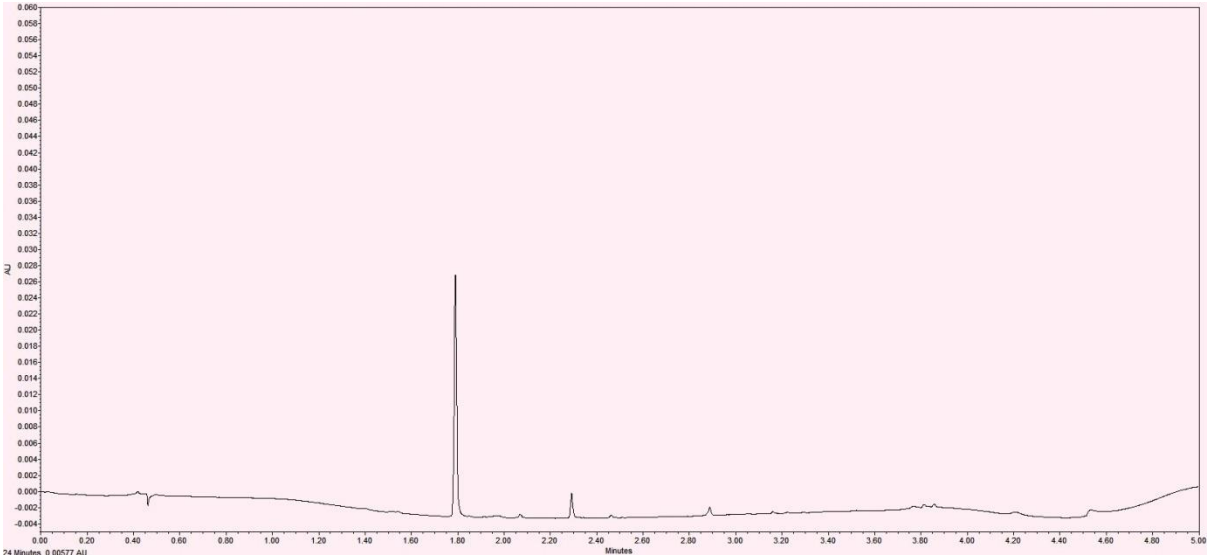


Figure 5. Salicylic acid chromatogram in UPLC analysis